

R E M A R K S

Status of the Application

Previously, Applicants had requested the Examiner to vacate the second Office Action (dated March 19, 2004) and provide action on the merits concerning the response of Applicants filed on March 19, 2004. However, the Examiner has indicated that the March 19, 2004 Amendment has been entered as a response to the February 25, 2004 Office Action and thus, the March 19, 2004 Office Action is to be treated as a Supplemental Office Action.

Applicants believe that many of the issues raised in the March 19, 2004 Office Action are technically moot in view of Applicants submission of March 19, 2004. However, in the present submission, Applicants intend to respond fully to the March 19, 2004 Office Action. This may include some duplication of arguments from the March 19, 2004 submission of record.

Status of the Claims

Claims 1-6, 8, 9, 11, 12, and 20-22 are pending. Applicants submit that no new matter has been added by way of the present amendment. For instance, claim 1 has been amended to remove reference to "functional GFP analogue." Claim 3 has been amended to correct the spelling of "Aequorea victoria" as requested by the Examiner. These amendments are non-narrowing in

nature. New claim 22 is supported by claims 1 and 4.

Accordingly, no new matter has been added.

In view of the following remarks, Applicants respectfully request that the Examiner withdraw all rejections and allow the currently pending claims.

Objections to the Claims

The Examiner has objected to the spelling of "Aequorea victoria" in claim 3. Applicants submit that this issue has been addressed in the present amendment. Thus, this objection is moot.

Issues under 35 U.S.C. § 112, first paragraph

The Examiner has rejected claims 1-6, 8, 9, 11, 12, 20 and 21 under 35 U.S.C. § 112, first paragraph for the reasons recited at pages 2-6 of the outstanding Office Action. Applicants respectfully traverse these rejections.

The Examiner's rejections can be separated into "written description", "enablement", and "additional" rejections, which will be discussed separately below.

1. Written Description Rejections

The Examiner asserts that there is insufficient "written description" for the modified GFP currently claimed. Applicants disagree and submit that this rejection fails to take into consideration the following amendments made on March 19, 2004:

- a) the substitution at position 1 preceding the chromophore was defined as being an aliphatic amino acid; and
- b) SEQ ID NO: 4 was used as a reference point for the claim.

However, the Examiner still appears to reject the "functional GFP analogue" language in the claims. Applicants submit that those of skill in the art understand that Applicants were in possession of "functional GFP analogues" at the time of filing. Several analogues of GFP are known, any of which could carry the substitutions recited, for instance, in claims 1 and 22. Applicants have removed the language relating to "functional GFP analogue" from the claims. However, Applicants submit that the term "GFP" already recited in the claim is in itself generic and thus, the removal of "functional GFP analogues" simply removes redundant textual subject matter. Accordingly, the amendment discussed above is non-narrowing in nature, and this issue is moot. Reconsideration and withdrawal thereof are respectfully requested.

2. Enablement Rejections

The Examiner further asserts that there exists insufficient enablement for the present claims. Similar to the above, Applicants submit that the Examiner's rejections do not take into account amendments a) and b) discussed above. With the exception of a single issue (discussed below), Applicants submit that the Examiner's rejections are rendered moot by the March 19, 2004 Amendment.

This one additional issue is that the Examiner has rejected the "functional GFP analogue" language in the claims. Applicants submit that those of skill in the art are fully aware of GFP and the analogues thereof. Thus, based upon the description of the present application, those of skill in the art can readily make and use GFP molecules having the claimed substitutions without undue experimentation. Accordingly, this issue is moot. Reconsideration and withdrawal thereof are requested.

3. Additional 35 U.S.C. § 112, first paragraph rejection

At page 6 of the outstanding Office Action, the Examiner asserts that claim 12 broadly reads on any kinase/cytoskeletal element, which is allegedly not supported by the disclosure. Applicants respectfully traverse this rejection and disagree with the Examiner.

Applicants draw the Examiner's attention to the fact that the embodiment of claim 12 is discussed at page 12, lines 15-18 of the specification. However, the Examiner has provided no legal basis as to why such subject matter is improper. Without further evidence from the Examiner, Applicants submit that this rejection is legally insufficient.

The Examiner has simply stated that the "kinase/cytoskeletal element" is not supported by the disclosure. Applicants have pointed out above that this is not accurate since this embodiment finds support at page 12, lines 15-18 of the present specification. Further, the Examiner asserts that the working examples do not demonstrate this embodiment. Applicants submit that there is not requirement for a working example of this embodiment. Accordingly, Applicants submit that this rejection is improper and should be withdrawn.

Issues under 35 U.S.C. § 112, second paragraph

The Examiner has rejected claims 1-6, 8, 9, 11, 12, 20 and 21 under 35 U.S.C. § 112, second paragraph for the reasons recited at pages 6-7 of the outstanding Office Action. Applicants respectfully traverse these rejections.

First, the Examiner asserts that claim 1 is indefinite for reciting "wherein the amino acid in position 1 preceding the

chromophore has been substituted." The Examiner also notes that the claims recite positions without referring to a reference sequence. However, Applicants draw the Examiner's attention to the fact that on March 19, 2004, claim 1 was amended to reflect that this substitution is an aliphatic amino acid substitution. Claim 1 was also amended to refer to SEQ ID NO:4 as a reference sequence. Thus, the issue is moot.

Second, the Examiner has rejected the language "functional analogue" as recited in claim 1. However, Applicants have already explained that those of skill in the art fully understand this terminology. However, in an effort to further prosecution, this term has been removed from the claims. Thus, this issue is moot.

Based upon the above, reconsideration and withdrawal of these rejections are respectfully requested.

Provisional Obviousness-type Double Patenting

The Examiner has rejected claims 1-6, 8, 9, 11, 12, 20 and 21 under the judicially created doctrine of obviousness-type double patenting as being obvious over claims 1-12 of copending application no.: 10/296,953. Applicants respectfully traverse this provisional rejection.

Neither the present claims nor the claims of copending application no.: 10/296,953 have been allowed. The present

"provisional" double patenting rejection should continue to be made by the Examiner in each application as long as there are conflicting claims in more than one application unless that "provisional" double patenting rejection is the only rejection remaining in one of the applications. If the "provisional" double patenting rejection in one application is the only rejection remaining in that application, the Examiner should then withdraw that rejection and permit the application to issue as a patent, thereby converting the "provisional" double patenting rejection in the other application into an obviousness-type double patenting rejection at the time the one application issues as a patent. See MPEP § 804(I)(B).

In the present instance, if the above "provisional" rejection is the only rejection remaining, Applicants request that, pursuant to MPEP § 804(I)(B), the Examiner withdraw this rejection and allow the present application to proceed to issuance.

Issues under 35 U.S.C. § 103(a)

The Examiner has rejected claims 1-6 and 8 under 35 U.S.C. 103(a) as being obvious over Thastrup et al., WO 97/11094 (hereinafter referred to as Thastrup) in view of Ehrig et al., FEBS Letters, Vol. 367, pages 163-166, 1995 (hereinafter referred to as Ehrig). Applicants respectfully traverse this rejection.

The Examiner asserts that the Thastrup article discloses the F64L mutation of GFP and the Ehrig reference discloses the E222G mutation of GFP. Applicants disagree with the Examiner's combination and reading of the cited art.

One embodiment of the present claims involves a combination of the F64L and E222G mutations of GFP. As described in the present specification, the F64L-E222G-GFP has an excitation maximum of 470 nm and an emission maximum of 505 nm (see Figure 3, and example 2 of the present specification).

In contrast, the GFP mutant described by Ehrig has an excitation maximum of 481nm and an emission maximum at 506nm (page 2, lines 14-16 of the present specification). It is clear from the Thastrup reference that the F64L mutation only alters the folding kinetics of GFP, not the spectral properties (see section starting on page 3, line 30 to page 4, line 6, and examples of the present application). Thus, one of ordinary skill in the art is provided with no suggestion that a combination of Thastrup and Ehrig, as proposed by Examiner, would result in a GFP product with this increased Stokes-shift.

A Stokes shift of 35 nm for F64L-E222G-GFP results in a significant increase in the excitation-emission band separation for F64L-E222G-GFP with several implications for the use of

F64L-E222G-GFP in high-throughput screening (see page 5, lines 1-15 of the present specification).

In summary, Applicants submit that even if it were hypothetically established that one of skill in the art would have been motivated to combine Thastrup with Ehrig as suggested by the Examiner, a point not conceded by Applicants, it is submitted that there is no suggestion of the unexpected and superior results achieved by the present invention. That is, there could have been no expectation of the increased Stokes shift of 35 nm for the presently claimed subject matter compared to the prior art. Thus, these unexpected and superior results rebut any hypothetical prima facie case of obviousness.

Additionally, Applicants point out that claim 1 requires that the amino acid immediately preceding the chromophore is substituted with an aliphatic amino acid. This is a further distinction over the cited art.

Accordingly, the disclosures of Thastrup and Ehrig, whether taken alone or in combination, fail to suggest or disclose the presently claimed subject matter, much less the unexpected results according to the present invention. Therefore, the Examiner is respectfully requested to withdraw all rejections and allow the currently pending claims.


If the Examiner has any questions or comments, please contact Craig A. McRobbie, Reg. No. 42,874, at the offices of Birch, Stewart, Kolasch & Birch, LLP.

Pursuant to 37 C.F.R. §§ 1.17 and 1.136(a), Applicant(s) respectfully petition(s) for a two (2) month extension of time for filing a reply in connection with the present application, and the required fee of \$420.00 is attached hereto.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37 C.F.R. §§1.16 or 1.17; particularly, extension of time fees.

Respectfully submitted,

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